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Infertility among Women Exposed Prenatally to Diethylstilbestrol

Julie R. Palmer,[1] Elizabeth E. Hatch,[2] R. Sowmya Rao,[1] Raymond H. Kaufman,[3] Arthur L. Herbst,[4] Kenneth L. Noller,[5] Linda Titus-Ernstoff,[6] and Robert N. Hoover[2]

Although it is well established that women exposed to diethylstilbestrol in utero have an increased risk of spontaneous abortion, ectopic pregnancy, and preterm delivery, it is not known whether they also have an increased risk of infertility. The authors assessed this question in data from a collaborative follow-up study of the offspring of women who took diethylstilbestrol during pregnancy. In 1994, 1,753 diethylstilbestrol-exposed and 1,050 unexposed women from an ongoing cohort study (National Cooperative Diethylstilbestrol Adenosis Study and Dieckmann cohorts) provided data on difficulties in conceiving and reasons for the difficulty. Age-adjusted relative risks were computed for the association of diethylstilbestrol exposure with specific types of infertility. A greater proportion of exposed than unexposed women were nulligravid (relative risk (RR) = 1.3, 95% confidence interval (CI): 1.1, 1.5), and a greater proportion had tried to become pregnant for at least 12 months without success (RR = 1.8, 95% CI: 1.6, 2.1). Diethylstilbestrol exposure was significantly associated with infertility due to uterine and tubal problems, with relative risks of 7.7 (95% CI: 2.3, 25) and 2.4 (95% CI: 1.2, 4.6), respectively. The present findings indicate that diethylstilbestrol-exposed women have a higher risk of infertility than do unexposed women and that the increased risk of infertility is primarily due to uterine or tubal problems. *Am J Epidemiol* 2001;154:316–21.

diethylstilbestrol; infertility

Women who were exposed to diethylstilbestrol in utero commonly have malformations of the uterus, cervix, and fallopian tubes, all of which are associated with a higher prevalence of unfavorable pregnancy outcomes (1–9). Spontaneous abortion, ectopic pregnancy, and preterm delivery are more common among diethylstilbestrol-exposed women (9). Whether diethylstilbestrol-exposed women also have more difficulty achieving pregnancy is unresolved. The two most informative previous studies on this question provide conflicting results (2, 10). The present study is based on the continued follow-up of the two cohorts previously studied (2, 10) and provides information on whether diethylstilbestrol-exposed women are at higher risk of infertility and, if so, which factors contribute to the infertility.

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Abbreviations: CI, confidence interval; DESAD, National Cooperative Diethylstilbestrol Adenosis Study; OR, odds ratio; RR, relative risk.

[1] Slone Epidemiology Unit, Boston University School of Medicine, Brookline, MA.
[2] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.
[3] Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX.
[4] Department of Obstetrics and Gynecology, University of Chicago, Chicago, IL.
[5] Department of Obstetrics and Gynecology, University of Massachusetts Medical Center, Worcester, MA.
[6] Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH.
Reprint requests to Dr. Julie R. Palmer, Slone Epidemiology Unit, Boston University School of Medicine, 1371 Beacon Street, Brookline, MA 02446 (e-mail: jpalmer@slone.bu.edu).

MATERIALS AND METHODS

Subjects

Two cohorts are included in the present study. The larger consists of women enrolled during the mid-1970s into the National Cooperative Diethylstilbestrol Adenosis (DESAD) Study (11). Exposed women were identified by review of prenatal records at five medical centers (Mayo Clinic, Rochester, Minnesota; Boston Lying-In Hospital, Boston, Massachusetts; Gunderson Clinic, LaCrosse, Wisconsin; Baylor College of Medicine, Houston, Texas; and the University of Southern California, Los Angeles, California). Unexposed women were selected from the same prenatal record sources as the exposed subjects or were sisters of exposed subjects; the prenatal records of their mothers contained no notations of diethylstilbestrol use. DESAD participants were actively followed with yearly physical examinations and interviews through 1984 and by mailed questionnaire from 1985 through 1989. DESAD participants who were enrolled as a result of physician or self-referral have been excluded from the present study.

The other cohort (Dieckmann cohort) includes women whose mothers participated in a randomized trial of the efficacy of diethylstilbestrol during pregnancy conducted at the University of Chicago (12). Eighty-three percent of exposed

and 77 percent of unexposed trial participants were located in 1974, and their daughters were followed episodically until 1990 (13, 14).

All exposed women had documented exposure to diethylstilbestrol during gestation, and for most there was information on the week of gestation when diethylstilbestrol was first taken. In general, the Dieckmann cohort daughters were exposed to higher doses of diethylstilbestrol than were the DESAD cohort daughters, with an average total dose of about 12 g. Dose information was not available on most DESAD participants; where known, it ranged from a median total dose of 1.5 g at Baylor College of Medicine and Mayo Clinic to 4.5 g at the Boston Lying-In Hospital.

In 1994, follow-up questionnaires were completed by 1,753 exposed (1,520 from DESAD, 233 from Dieckmann) and 1,050 unexposed (840 from DESAD, 210 from Dieckmann) study subjects. These numbers represent 81 percent of exposed subjects and 81 percent of unexposed subjects originally identified from review of the medical records of the DESAD project and 56 percent of exposed subjects and 53 percent of unexposed subjects from the Dieckmann cohort.

The present study was approved by the Institutional Review Board of Boston University Medical Center, as well as by the review boards of the other collaborating institutions.

Data collection

The 1994 questionnaire included questions on demographic factors, health outcomes, and reproductive history. Subjects were asked if they had ever tried to become pregnant for 12 months or more without success; whether they had ever seen a physician because of difficulty getting pregnant; whether the infertility was due to a female factor, male factor, or both; and the final diagnosis. For diagnosis, subjects could check "ovulatory problem," "endocrine (hormonal) problem," "uterine problem," "tubal problem," "other problem (specify)," "unexplained infertility," or "don't know." Subjects were also asked about the use of fertility drugs or assisted reproductive technologies.

A validation study of self-reported infertility was conducted. Sixty-three participants who had reported infertility were selected such that all centers and all diagnoses were represented approximately equally, and 36 gave permission for review of medical records. The treating physician was asked to complete a one-page medical record abstract form. Completed medical record abstracts were obtained for 29 participants. Of these, 26 (90 percent) confirmed the diagnosis reported by the participant. Based on these results and the difficulty of obtaining consent to review records, we decided to rely on self-reported outcomes.

Statistical analysis

Relative risks (ratio of cumulative incidences of exposed and unexposed) were computed for the association of diethylstilbestrol exposure with infertility overall and for specific types of infertility. "Ovulatory problem" and "hormonal problem" were combined into one category because so many women reported both. Women who had unexplained infertility or who did not know the diagnosis were grouped together. Endometriosis was the most common of specified "other problems" and was analyzed separately. Relative risks were adjusted for year of birth by a Mantel-Haenszel analog, which uses stratum-specific sample sizes as the weight (15); the adjusted relative risks are presented in all the tables and in the text. Further adjustment for marital status, years of education, age at menarche, use of oral contraceptives, and two measures of health care behaviors did not materially change the estimates.

RESULTS

The median age in 1994 was 42 years (table 1). Exposed and unexposed subjects were similar with regard to years of education, marital status, cigarette smoking, and frequency of mammograms. Exposed women had reported more Papanicolaou smear tests in the past 5 years.

Twenty-four percent of exposed and 18 percent of unexposed women had never become pregnant (relative risk (RR) = 1.3, 95 percent confidence interval (CI): 1.1, 1.5) (table 2).

TABLE 1. Characteristics of diethylstilbestrol-exposed and unexposed participants, DESAD* and Dieckmann cohorts, mid-1970s–1994

	Exposed	Unexposed
Median age in 1994 (years)	42	42
Marital status in 1994 (%)		
Never married	13	13
Ever married	87	87
Years of education (%)		
≤12 years	16	18
Some college	27	24
College graduate	57	58
Cigarette smoking in 1994 (%)		
Never	58	53
Current	16	15
Past	26	32
No. of Papanicolaou tests in past 5 years (%)		
0, 1	11	10
2, 3	24	28
4	48	51
≥5	17	10
No. of mammograms in past 5 years (%)		
0	26	22
1	28	30
≥2	44	46
DESAD cohort (%)	87	80
Dieckmann cohort (%)	13	20

* DESAD, National Cooperative Diethylstilbestrol Adenosis Study.

Twenty-eight percent of exposed and 16 percent of unexposed women reported having tried to become pregnant for at least 12 months without success (RR = 1.8, 95 percent CI: 1.6, 2.1). Among those who reported difficulty conceiving, approximately equal proportions (18 percent of exposed and 16 percent of unexposed women) never underwent evaluation for infertility, and they are not considered further. A total of 183 exposed and 48 unexposed women had undergone evaluation for infertility before ever becoming pregnant (primary infertility), 119 exposed and 38 unexposed women had already had at least one pregnancy before evaluation for infertility (secondary infertility), and the remainder did not provide dates for the diagnosis. Diethylstilbestrol exposure was associated with both primary (RR = 2.5) and secondary (RR = 2.0) infertility and was not associated with male factor infertility.

The analyses were repeated with exposed women grouped according to gestational age at first exposure to diethylstilbestrol (table 3). The relative risk for never pregnant was highest for those exposed before 9 weeks (RR = 1.5, 95 percent CI: 1.3, 1.8) and lowest for those first exposed at 13 weeks or later (RR = 1.1, 95 percent CI: 0.9, 1.3). For women ever trying to become pregnant for at least 12 months without success, the relative risks were 1.9 and

TABLE 2. Pregnancy and infertility among diethylstilbestrol-exposed and unexposed women, DESAD* and Dieckmann cohorts, mid-1970s–1994

	Exposed (n = 1,753)		Unexposed (n = 1,050)		Age-adjusted relative risk	95% Confidence interval
	No.	%	No.	%		
Pregnancy						
Ever pregnant	1,325	76	859	82	Reference	
Never pregnant	422	24	189	18	1.3	1.1, 1.5
Unknown	6		2			
Infertility						
Ever tried to become pregnant for ≥12 months without success						
No	1,260	72	884	84	Reference	
Yes†	493	28	166	16	1.8	1.6, 2.1
Male factor infertility	24		10		1.5	0.8, 2.8
Primary infertility‡	183		48		2.5	1.8, 3.3
Secondary only§	119		38		2.0	1.5, 2.8
Infertility of unknown timing¶	80		43		1.2	1.0, 1.5
Mean age at infertility diagnosis (years)	33 (7.7)#		33 (8.0)			

* DESAD, National Cooperative Diethylstilbestrol Adenosis Study.
† Of those who responded "yes" to ever trying to become pregnant for ≥12 months without success, 87 exposed and 27 unexposed women never underwent evaluation for infertility.
‡ Infertile women were considered to have primary infertility if they never became pregnant or were diagnosed with infertility before their first pregnancy.
§ Infertile women were considered to have secondary infertility if their earliest diagnosis of infertility was after the year of their first pregnancy.
¶ From the information provided, it was not possible to determine whether or not the infertility preceded the first pregnancy.
# Numbers in parentheses, standard deviation.

TABLE 3. Pregnancy and infertility according to timing of diethylstilbestrol exposure, DESAD* and Dieckmann cohorts, mid-1970s–1994

	No.	% Never pregnant	Age-adjusted relative risk	95% Confidence interval	% Reported infertility†	Age-adjusted relative risk	95% Confidence interval
Unexposed	1,050	18.0	Reference		15.8	Reference	
Gestational age at first exposure to DES* (weeks)							
<9	503	30.2	1.5	1.3, 1.8	28.2	1.9	1.5, 2.3
9–12	498	21.9	1.2	0.9, 1.4	31.5	2.0	1.7, 2.5
≥13	648	20.5	1.1	0.9, 1.3	25.5	1.6	1.3, 2.0
Unknown	104	26.9	1.3	0.9, 1.9	27.9	2.2	1.5, 3.2

* DESAD, National Cooperative Diethylstilbestrol Adenosis Study; DES, diethylstilbestrol.
† Infertility defined as ever tried to become pregnant for at least 12 months without success.

2.0 for exposure before the ninth week and at 9–12 weeks' gestation, respectively, and lower (RR = 1.6) for exposure after the first trimester.

Diethylstilbestrol exposure was most strongly associated with infertility due to uterine problems (odds ratio (OR) = 7.7, 95 percent CI: 2.3, 25) (table 4). Exposure was also associated with infertility due to tubal problems, more than one type of problem, and unknown type of infertility. Sixty-five of the 78 participants who were classified as having more than one type of problem had reported a tubal or uterine problem for at least one of their infertility diagnoses (data not shown). Diethylstilbestrol exposure was not significantly associated with other causes of infertility. The relative risk for the association of diethylstilbestrol exposure with infertility due to ovulatory or hormonal problems was 1.3 (95 percent CI: 1.0, 1.9).

We repeated the analyses, considering only women with primary infertility (table 4). Similar associations were observed for the various types of infertility as in the overall data.

The results were similar among the DESAD cohort and the Dieckmann cohort and were unchanged after exclusion of women who had never been married (data not shown).

Similar proportions of exposed and unexposed women reported use of ovulation-inducing drugs (table 5). The relative risk for the association of diethylstilbestrol exposure with use of in vitro fertilization or other assisted reproductive technologies (other than artificial insemination) was elevated but not statistically significant (OR = 1.7, 95 percent CI: 0.9, 3.4).

Although overall more exposed than unexposed women never became pregnant (24 percent vs. 18 percent; table 1), approximately equal proportions of exposed and unexposed (51 percent vs. 52 percent) women who reported primary infertility eventually achieved a pregnancy.

DISCUSSION

The results of the study indicate that diethylstilbestrol-exposed women are more likely than are unexposed women

TABLE 4. Reason for infertility among diethylstilbestrol-exposed women,* DESAD† and Dieckmann cohorts, mid-1970s–1994

	All infertile women				Primary infertility only			
	Exposed (no.)	Unexposed (no.)	Age-adjusted relative risk	95% Confidence interval	Exposed (no.)	Unexposed (no.)	Age-adjusted relative risk	95% Confidence interval
Never tried to become pregnant for at least 12 months without success	1,260	884	Reference		1,260	884	Reference	
Had difficulty conceiving because of								
Uterine problem	24	2	7.7	2.3, 25	9	1	7.2	1.3, 41
Tubal problem	33	9	2.4	1.2, 4.6	22	1	16	3.6, 71
Hormonal/ovulatory problem	57	28	1.3	1.0, 1.9	28	18	1.1	0.8, 1.4
Endometriosis	17	9	1.2	0.7, 1.9	13	8	1.1	0.7, 1.9
"Other" problem	13	3	2.6	0.8, 8.1	4	3	0.8	0.1, 9.5
More than one type of problem	64	14	3.0	1.7, 5.1	46	7	4.4	2.1, 8.8
Unknown type	174	64	1.7	1.4, 2.2	61	10	4.1	2.3, 7.6

* Women who had difficulty conceiving but never underwent evaluation for it and women whose infertility was due to a problem with her partner are excluded.

†DESAD, National Cooperative Diethylstilbestrol Adenosis Study.

TABLE 5. Use of fertility drugs and assisted reproductive technologies among diethylstilbestrol-exposed and unexposed women who reported difficulty conceiving, DESAD* and Dieckmann cohorts, mid-1970s–1994

	Exposed (n = 493)		Unexposed (n = 166)		Age-adjusted relative risk	95% Confidence interval
	No.	%	No.	%		
Ever use of ovulation-induction medication						
No	294	60	104	63	Reference	
Yes	199	40	62	37	1.0	0.8, 1.1
Use of assisted reproductive technologies						
No	387	79	140	84	Reference	
Artificial insemination only	51	10	16	9.6	1.0	0.8, 1.3
In vitro fertilization and/or other procedures	55	11	10	6.0	1.7	0.9, 3.4

* DESAD, National Cooperative Diethylstilbestrol Adenosis Study.

to have difficulty achieving a clinically recognized pregnancy and more likely to have tried to become pregnant for at least 12 months without success. Diethylstilbestrol exposure was associated with primary infertility, secondary infertility, and with never becoming pregnant. Among the possible causes of infertility, diethylstilbestrol exposure was most strongly associated with infertility due to uterine problems, tubal problems, and more than one type of problem, which usually included either uterine or tubal problems. Diethylstilbestrol exposure was only weakly associated with infertility due to ovulatory or hormonal factors (RR = 1.3), and the estimate was not statistically significant. Most of the increased risk of never becoming pregnant was confined to women whose mothers took diethylstilbestrol before the ninth week of gestation. For infertility, the increased risk was concentrated in those exposed in the first trimester, but a smaller increase was also observed for those exposed later in pregnancy. These results are consistent with earlier findings from the DESAD Study of an increased prevalence of structural anomalies among women exposed in the first trimester of pregnancy (16).

The present findings of increased infertility among diethylstilbestrol-exposed women are consistent with previous findings from the Dieckmann cohort, in which 33 percent of diethylstilbestrol-exposed women had difficulty conceiving as opposed to 14 percent of unexposed women (10). The findings do not accord, however, with previous findings from the DESAD cohort (2, 17): approximately equal proportions of exposed and unexposed participants (about 50 percent) had become pregnant at least once. A third smaller study also found no difference in the proportions of nulligravid women among exposed and unexposed women (4). These differences in findings may be explained by the fact that all three studies evaluated women who were still early in their reproductive life. For example, in the comparison of 618 exposed and unexposed women from the DESAD cohort, 47 percent had not yet reached the age of 25 years, and 87 percent had not yet reached 30 years. The present analysis, which includes both the DESAD cohort and the Dieckmann cohort, is considerably larger (with 1,753 exposed women) and assesses women who are near the end of their reproductive years.

Previous results concerning the effects of uterine and tubal abnormalities on the reproductive experience of diethylstilbestrol-exposed women have been more consistent. Senekjian et al. (10) found that, among those who underwent evaluation for primary infertility, tubal defects and abnormal hysterosalpingograms were the factors found more often in diethylstilbestrol-exposed women. Kaufman et al. (1, 18) found that women who had a constricted upper portion of the uterus were more likely to have difficulty conceiving, and Berger and Alper (19) found a markedly reduced fertility in diethylstilbestrol-exposed women with abnormal findings on hysterosalpingograms. In the present study, diethylstilbestrol exposure was most strongly associated with infertility due to tubal defects, uterine problems, and more than one type of problem, which usually included a tubal or uterine problem. Structural abnormalities in the fallopian tubes and uterus can lead to infertility in a number of ways: altered tubal motility, constricted or nonpatent tube, deficient endometrial surface for implantation, myometrial dysfunction, cervical stenosis, and poor production of cervical mucus.

Senekjian et al. (10) did not find an increased prevalence of ovulatory factors or endometriosis among diethylstilbestrol-exposed women who underwent evaluation for primary infertility. Similarly, Stillman and Miller (20) found little difference in the prevalence of endometriosis among diethylstilbestrol-exposed women and unexposed women who were evaluated for infertility. In contrast, Berger and Alper (19) found a significant difference in the prevalence of endometriosis among exposed and unexposed infertile women, with exposed women experiencing about 50 percent more endometriosis. In the present study, which is considerably larger than previous efforts, diethylstilbestrol exposure was not associated with an increased risk of primary infertility due to ovulatory or hormonal factors, and similar proportions of exposed and unexposed women had ever taken ovulation-inducing drugs. These findings are of interest because previous evidence of ovulatory dysfunction and menstrual irregularities in diethylstilbestrol-exposed women had raised the hypothesis that hormonal or ovulatory factors may contribute to a reduced fecundity among diethylstilbestrol-exposed women (7). It was also hypothesized that diethylstilbestrol-exposed women may be more likely to develop endometriosis due to cervical stenosis with resulting backflow of menstrual blood (20). The present results indicate that endometriosis is no more likely to be a major contributing factor to infertility in exposed women than in unexposed women.

Certain limitations of the present study should be noted. The first is a possible selection bias. Although follow-up was complete on 81 percent of both exposed and unexposed women from the DESAD cohort, only 56 percent of exposed and 53 percent of unexposed women from the Dieckmann cohort participated. If participation was related to both exposure status and ever having difficulty becoming pregnant, this could have biased the results. However, about half of the Dieckmann cohort nonparticipants were daughters who had never been located and given an opportunity to participate; it is unlikely, therefore, that their participation would be differential on infertility status.

Second, the analyses relied on data from self-reports, and not all participants will have remembered their infertility diagnosis accurately. In our validation study, we confirmed the reason for infertility reported by 26 of 29 participants whose records were obtained. However, only 57 percent of those approached gave permission for review of their records. If women who gave permission were more likely to have reported their infertility correctly, there may have been more misclassification of diagnosis than it appears.

Diethylstilbestrol-exposed women may have been more likely to be evaluated for infertility or to have received a more intensive workup. This could have resulted in an overestimation of the relative risk for the association of diethylstilbestrol exposure with physician-diagnosed infertility. However, approximately equal proportions of exposed (82 percent) and unexposed (84 percent) participants who

reported difficulty in conceiving underwent evaluation for the problem. Furthermore, the fact that only about 50 percent of those who reported primary infertility were able to ever become pregnant lends credibility to the self-reporting of difficulty in becoming pregnant. The similarity of eventual success in the exposed and unexposed women implies a lack of significant bias; that is, the exposed were not more likely to have reported trivial difficulties that were not really reflective of a problem. Nevertheless, it is impossible to rule out this potential bias, and it may explain the slightly elevated point estimates observed for male factor infertility (which would be expected to be 1.0) and for infertility due to ovulatory or hormonal factors.

Of more concern is a potential detection bias whereby exposed daughters may have been more likely to have their infertility attributed to uterine or tubal factors, either because they were subjected to a more invasive workup or because of a lack of other specific findings. Infertility diagnoses are complex, and it is likely that infertility specialists knew their patients' diethylstilbestrol history. If such a bias occurred, the relative risks observed for tubal and uterine problems may overestimate the true association.

In summary, the present study, which is larger and includes a considerably longer follow-up period than any previous study, indicates that women exposed to diethylstilbestrol in utero have an increased risk of infertility, both primary and secondary, and that the increase is primarily due to tubal and uterine factors.

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